

A.K.  
R**Title**

RF2062 Mist  
Request for Waiver of a Pesticide Data Requirement

**Data Requirement**

*Health Effects Test Guidelines - OPPTS Series 870*  
Companion Animal Safety – OPPTS 870.7200

**Author**

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**Study Number**

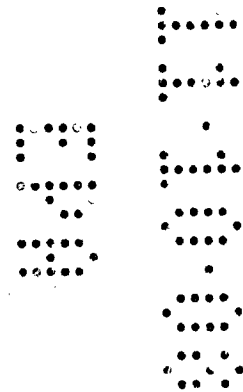
3509

**Date Completed**

7 October 2008

**Submitted by:**

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1501 East Woodfield Road  
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## STATEMENT OF NO DATA CONFIDENTIALITY CLAIMS

No claim of confidentiality is made for any information contained in this study on the basis of its falling within the scope of FIFRA 10(d)(1)(A), (B) or (C).

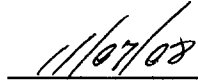
**Company:** Wellmark International

**Company Agent:**



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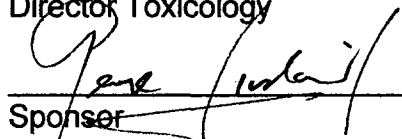
These data are the property of Wellmark International, and, as such, are considered confidential for all purposes other than compliance with FIFRA Section 10. Submission of these data in compliance with FIFRA does not constitute a waiver of any right to confidentiality that may exist under any other statute or in any other country.

## GOOD LABORATORY PRACTICES STATEMENT


This study does not meet the requirements of 40 CFR Part 160, and differs in the following ways:

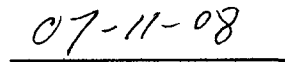
1. It is not a laboratory study.
2. It did not have a Study Director.

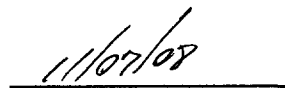
  
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## **Request for Waiver Pesticide Data Requirement for RF 2062 Mist:**

The RF2062 Mist is a new me-too pet spray product from Wellmark International. The product will be packaged as a pump spray. RF 2062 Mist contains pyrethrins as the active ingredient and piperonyl butoxide (PBO) and N-octyl bicycloheptene dicarboximide (MGK-264) as synergists. Pyrethrins are registered for use in agricultural, residential, commercial, industrial, and public health sites. It is common to combine preparations containing pyrethrin with synergists such as PBO and MGK-264 to increase activity.

The percentages of active ingredients in the finished product are shown below:

Pyrethrins (CAS# 8003-34-7).....	0.20%
Piperonyl butoxide (CAS# 51-03-6) .....	0.37%
N-octyl bicycloheptene dicarboximide (CAS# 113-48-4).....	0.62%

The EPA has requested companion animal safety studies for adult cats and dogs as well as juvenile animals (12 weeks of age) for both species.

Rf2062 Mist is very similar to the registered formulation RF9606 (EPA Reg. No. 2724-404). The major difference between the two formulations is that RF9606 contains methoprene which RF2062 Mist does not. RF2062 Mist contains a small amount of fragrance that RF9606 does not have. All other components of the formulation are identical. While there are no companion animal safety studies specific to RF9606 available, RF9606 has an extensive database on the adverse reactions in canines and felines showing low toxicity to the formulation. Based on the adverse reaction data for RF9606 a request for a data waiver for cats and kittens and dogs and puppies is made.

The following data waiver for a pesticide data requirement is requested for RF2062 Mist:

Companion Animal Safety (OPPTS 870.7200)

**OPPTS Guideline:** 870.7200  
**Data Requirement:** Companion Animal Safety

**Summary:**

RF2062 Mist is a pet spray formulation that will be packaged as a pump spray. The formulation contains 0.20% pyrethrins, 0.37% piperonyl butoxide and 0.62% N-octyl bicycloheptene dicarboximide (MGK-264).

**Waiver Rationale:**

The formulations for RF9606 and RF2062 Mist are presented in Table 1. The RF9606 formulation is very similar to the RF2062 Mist formulation. The major difference between the two formulations is that RF2062 Mist contains no methoprene. The only other difference is a small amount of fragrance has been added to RF2062 Mist. All other components of the formulation are identical. Based on the similarity of the formulations and the low mammalian toxicity of methoprene, it would be expected that the toxicity of the two formulations to canines and felines would be very similar.

As part of the EPA FIFRA adverse reaction reporting Wellmark International maintains a comprehensive database of all reported adverse reactions to their products and evaluates them for relevance to the product taking into consideration the use of the product according to label directions, the types of symptoms reported and when they occurred relative to the application, and any known disease conditions of the animal.

Table 2 summarizes the clinical signs reported for RF9606 by species and age as well as the severity of the reaction. This table shows the number of clinical signs and not the number of animals. Because an animal may be reported with multiple signs, the number of animals involved is actually less.

**Canine**

Clinical signs in dogs were reported 413 times, of these 67 were for puppies and the age was not known for 9. Nine deaths were attributed to RF9606, 3 adults and 6 puppies. Review of the case reports indicated that 5 of the 6 puppy deaths were from extra-label use (animals <12 weeks of age) and the other death was classified as "doubtful" with respect to its relationship to the product. All of the adult deaths were classified as "other disease suspected". All of the major adverse reactions were for adult dogs and the relationship to the formulation was considered "doubtful" in all cases.

The most frequently observed clinical signs are summarized in Tables 3 and 4 for minor and moderate signs, respectively. The minor reactions covered a wide range of clinical signs. The most frequently reported signs were vomiting, anorexia, depression/lethargy, pruritis, hypersalivation, erythema and bloody diarrhea. All were reported less than 30 times in adult animals over the three year period. Vomiting was reported 12 times in puppies and all other signs occurred eight times or less. The most common moderate observations were ataxia, hind limb weakness and clonic muscle tremors. Only ataxia was reported more than 10 times and only in adults.

### Felines

As shown in Table 2 clinical signs in cats were reported 1075 times, of these 285 were in kittens and the age was unknown for 20. Twenty-eight deaths were attributed to RF9606, 13 adults and 15 kittens. Fourteen of the 15 kitten deaths were from extra-label use (animals <12 weeks of age) and the other death was classified as "doubtful" with respect to its relationship to the product. Of the 13 adult cat deaths, four were extra-label uses and all others were considered "doubtful" for association to the product.

Major clinical signs were reported for 14 adult cats (including unknown age) and 7 kittens. Of the 7 kittens 6 were extra-label uses (animals <12 weeks of age) and the other one was classified as "doubtful". All of the adults with major clinical signs were either extra-label or "doubtful".

The most frequently observed clinical signs in cats and kittens are summarized in Tables 5 and 6 for minor and moderate signs, respectively. The minor adverse reactions covered a wide range of clinical signs. Approximately 50% of the reported signs were hypersalivations in both cats and kittens, a common observation in cats with any product. Other observations included depression/lethargy, vomiting, anorexia, hiding and trembling. The most common moderate observations were ataxia, hind limb weakness and clonic muscle tremors. Ataxia was reported 39 times in adults and 13 times in kittens. Hind limb weakness and muscle tremors were reported less than 15 times over the three year period.

The frequency with which reactions were reported was estimated from how many units (spray bottles) were sold. Each spray bottle contains between 10 and 15 applications. During the selected time period approximately 300,000 units were sold which would give at least 3,000,000 applications (doses). The product is a spray for cats and dogs. Information is not available for how many units are used on dogs and how many on cats. Assuming equal numbers of cats and dogs were treated with the product, 1,500,000 applications were made to adult dogs and puppies and an equal number to felines. Summarized in the table below are the number of animals reported with symptoms and the percent of animals with reactions relative to the total number of applications (doses) sold. As noted above, this includes extra-label uses and those cases where symptoms and medical history of the pet were not consistent with the toxicity of the active ingredients.

<b>Number of Animals with Clinical Signs</b>		
	<b>Number of Animals</b>	<b>Percent of Total Doses Sold</b>
<b><u>Canine</u></b>		
Adult dogs <sup>1</sup>	154	0.010%
Puppies <sup>2</sup>	39	0.003%
	<b>193</b>	<b>0.013%</b>
<b><u>Feline</u></b>		
Adult cats <sup>1</sup>	462	0.031%
Kittens <sup>2</sup>	187	0.012%
	<b>649</b>	<b>0.043%</b>

<sup>1</sup>Includes animals of unknown age

<sup>2</sup>Animals <6 months of age

In summary, a data waiver is requested for companion animal safety studies with RF2062 Mist based on the adverse reaction data collected for RF9606. For RF9606 for a three year period (January 2004 – February 2008) the number of clinical signs represented a very small fraction of the number of doses sold for both canines and felines. For dogs and puppies, clinical signs were reported for 0.013% of the doses sold and for cats and kittens, 0.043%. The majority of reported clinical signs were minor, 77% for dogs and puppies and 81% for cats and kittens.

The RF9606 formulation is very similar to the RF2062 Mist formulation. The major difference between the two formulations is that RF9606 contains methoprene. It would not be expected that RF2062 Mist would be more toxic than RF9606. With the low fraction of clinical signs reported relative to the doses sold and the types of reactions reported, it is highly unlikely that companion animal safety studies with RF2062 Mist would add any significant knowledge to the safety of the product to cats and dogs. For the above reasons a data waiver is requested for dogs (adults and puppies) and for cats (adults and kittens).

**Table 1**

**RF2062 Mist and RF9606 Formulations**

	RF2062 Mist	RF9606 EPA Reg. No. 2724-404
Pyrethrins	0.20	0.20
PBO	0.37	0.37
MGK-264	0.62	0.62
Methoprene		0.27



**Table 2**

**Summary of Number of Clinical Signs Reported with RF9606<sup>1</sup>  
January 2005 to February 2008**

	<u>Minor</u>	<u>Moderate</u>	<u>Major</u>	<u>Death</u>
<b><u>Canine</u></b>				
Adult dogs	258	68	8	3
Puppies	52	9	0	6
Unknown age	8	1	0	0
	<b>318</b>	<b>78</b>	<b>8</b>	<b>9</b>
<b><u>Feline</u></b>				
Adult cats	641	103	13	13
Kittens	222	41	7	15
Unknown age	13	6	1	0
	<b>876</b>	<b>150</b>	<b>21</b>	<b>28</b>

<sup>1</sup>Shown are the number of signs reported, not the number of animals. An animal may be reported with multiple signs. See the text table for the number of animals.

**Table 3**

**Minor Clinical Signs Reported in Adult Dogs and Puppies Treated with RF9606  
January 2005 to February 2008**

	<b>Times Reported in Adult Dogs<sup>1</sup></b>	<b>Times Reported in Puppies<sup>2</sup></b>
Projectile Vomiting	28	12
Depression Lethargy	22	5
Anorexia	22	6
Pruritis	18	3
Hypersalivation	17	1
Erythema	14	2
Bloody Diarrhea	13	8
Trembling	9	2
Acute Moist Dermatitis	7	0
Urticaria	5	1
Sneezing	4	1
Agitation	3	1
Restlessness	3	0
Polydipsia	3	1
Hiding	2	0
Vocalization	2	2
Retching/gagging	2	0
Hyperactivity	2	0
Ear Twitching	0	1

<sup>1</sup>Includes animals of unknown age

<sup>2</sup>Animals <6 months of age

**Table 4**

**Moderate clinical Signs Reported in Adult Dogs and Puppies Treated with RF9606  
January 2005 to February 2008**

	<b>Times Reported in Adult Dogs<sup>1</sup></b>	<b>Times Reported in Puppies<sup>2</sup></b>
Ataxia	11	0
Hind Limb Weakness	7	2
Clonic Muscle Tremors	5	2
CNS depression	4	0
Abdominal Distension	3	0
Mucopurulent Ocular Discharge	2	0
Disorientation	2	0
Mydriasis	2	0
Tachycardia	2	0
Fasciculation	1	0
Dyspnea	1	0

<sup>1</sup>Includes animals of unknown age

<sup>2</sup>Animals <6 months of age

**Table 5**

**Minor Clinical Signs Reported in Adult Cats and Kittens Treated with RF9606  
January 2005 to February 2008**

	<b>Times Reported in Adult Cats<sup>1</sup></b>	<b>Times Reported in Kittens<sup>2</sup></b>
Hypersalivation	308	117
Depression Lethargy	70	21
Projectile Vomiting	42	10
Anorexia	29	6
Hiding	28	3
Trembling	17	6
Paw shaking	9	6
Vocalization	9	3
Agitation	8	10
Recumbent	8	0
Ear Twitching	7	2
Retching/gagging	7	1
Flea Infestation	5	7
Pruritis	4	1
Sneezing	4	1
Hyperactivity	3	2
Restlessness	3	0
Bloody Diarrhea	2	2
Acute Moist Dermatitis	2	0
Polydipsia	2	0

<sup>1</sup>Includes animals of unknown age

<sup>2</sup>Animals <6 months of age

**Table 6**

**Moderate Clinical Signs Reported in Adult Cats and Kittens Treated with RF9606  
January 2005 to February 2008**

	<b>Times Reported in Adult Cat<sup>1</sup></b>	<b>Times Reported in Kittens<sup>2</sup></b>
Ataxia	39	13
Clonic Muscle Tremors	13	6
Hind Limb Weakness	11	6
Mydriasis	5	0
CNS depression	3	3
Fasciculation	3	2
Mucopurulent Ocular Discharge	3	1
Pale Mucous Membrane Color	3	2
Tachycardia	2	0
Dyspnea	2	1
Disorientation	1	0
Abdominal Distension	0	4

<sup>1</sup>Includes animals of unknown age

<sup>2</sup>Animals <6 months of age